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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
VIVLEMORE, TRACY ANN	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/510,667
Filing Date: April 05, 2005
Appellant(s): RAVIKUMAR ET AL.

Robert S. Andrews
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 24, 2009 appealing from the Office action mailed November 25, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 6,033,909 Uhlmann 3-2000

Kostenko et al. "5'-bis-pyrenylated oligonucleotides displaying excimer fluorescence provide sensitive probes of RNA sequence and structure" Nucleic Acids Research 2001, vol. 29, pages 3611-3620

Hamma et al. "Syntheses of Alternating Oligo-2'-O-Methylribonucleoside Methylphosphonates and Their Interactions with HIV TAR RNA" Biochemistry 1999, vol. 38, pages 15333-15342

Sproat et al. "The synthesis of protected 5'-mercapto-2',5' -dideoxyribonucleoside-3'-O-phosphoramidites; uses of 5' -mercapto-oligodeoxyribonucleotides" Nucleic Acids Research 1987, vol. 15, pages 4837-4848

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 4, 11-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann, Kostenko et al., Hamma et al., and Sproat et al.

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide and comprising a hydroxyl or protected hydroxyl at the 3' terminus. Claim 4 is directed to an embodiment wherein one position of the terminal phosphate is methylated. Claims 11-14 are directed to embodiments wherein the oligonucleotide is DNA, RNA or has 2' substituted sugars. Claims 15-18 recite limitations regarding the presence of a phosphorothioate backbone, the heterocyclic base moieties and the length of the oligonucleotide. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Uhlmann et al. teach oligonucleotides having formula 1 (see column 3 and claim 1). In this formula, the internucleotide linkages can be mono- or diphosphorothioate. The V at the 5' position of the ribose can be S and the terminal R^1 can be a phosphate group, which is the equivalent of the phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide of claim 1. The Z position of the terminal phosphate groups can be C_1-C_{18} alkyl, meeting the limitation of claim 4. In

the oligonucleotides disclosed by Uhlmann et al., R^2 can be hydrogen, hydroxyl or other substituents, meeting the limitations of claims 11-14. Position B is disclosed as being a conventional nucleotide base, meeting the limitations of claim 16. The oligonucleotides of Uhlmann et al. are 2-101 nucleotides in length, meeting the limitations of claims 17 and 18 and are disclosed in claim 9 as compositions with pharmaceutically acceptable carrier or diluent, meeting the limitations of claim 20. At column 4, line 39 through column 5, line 3 Uhlmann et al. teach that preferred oligonucleotides have oxo substituents at Y, V and X. Uhlmann et al. do not explicitly teach oligonucleotides having a hydroxyl or protected hydroxyl at the 3' terminus, but do teach at column 8, lines 55-62, that solid phase synthesis of oligonucleotides by the standard phosphoramidite method produces oligonucleotides with a 3'-hydroxyl group because the first nucleotide unit is bound to the solid support via the 3'-hydroxyl group.

Kostenko et al. teach 5'-bis-pyrenylated oligonucleotides produced by conjugating pyrene to a 5' phosphorylated oligonucleotide for the purpose of producing a fluorescent probe that can quantitatively detect hybridization. Kostenko et al. teach that these oligonucleotides were synthesized by standard phosphoramidite chemistry, which, as described by Uhlmann et al., produces a 3' hydroxyl group.

Hamma et al. teach that producing an oligonucleotide having a 5' phosphate allows a convenient "affinity handle" for purification by strong anion exchange HPLC. The oligonucleotides taught by Hamma et al. comprise 3' hydroxyls. In view of these teachings, one of ordinary skill in the art would recognize that predictable synthesis of

oligonucleotides having a 5' phosphate is routine and this technique is used for a variety of different reasons.

Sproat et al. teach the synthesis of 5'-mercapto-2', 5'-dideoxyribonucleoside phosphoramidites that can be used to produce oligonucleotides wherein the 5' oxygen is replaced with sulfur. Because these modified nucleotides are in a form suitable for automated nucleic acid synthesis, these monomers can be substituted at any position within an oligonucleotide, including the 5' terminus. Use of these monomers in a standard synthesis protocol produces oligonucleotides having 3' hydroxyls.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce oligonucleotides comprising 5' mercapto nucleotides and a 5' phosphate as taught by Uhlmann et al. and to make such an oligonucleotide comprising a 3' hydroxyl. Use of standard phosphoramidite synthesis, which, as evidenced by each of the cited references, is conventional in the art, will produce oligonucleotides having 3' hydroxyl groups. Based on the teaching of Sproat et al. of 5' mercapto nucleoside phosphoramidites suitable for incorporation at any point in a synthetic oligonucleotide, one of ordinary skill in the art would recognize the use of this particular monomer to be a matter of simple substitution of known equivalents that would predictably provide the 5' mercapto oligonucleotides that are taught by Uhlmann et al. Based on the teachings of Kostenko et al. and Hamma et al. one of ordinary skill in the art recognizes that synthesis of 5' phosphate oligonucleotides is routine in the art, therefore the synthesis of oligonucleotides comprising both a 5' mercapto nucleotide

and a 5' phosphate is a matter of design choice made in the course of routine optimization using equivalent elements known to those of ordinary skill in the art.

Thus, the invention of claims 1, 4, 11-18 and 20 would have been obvious, as a whole, at the time the invention was made.

(10) Response to Argument

Appellants state that the Federal Circuit has provided a two step analysis as the current standard of obviousness for new chemical compounds. This two-step analysis includes a determination whether one skilled in the art would have had a reason to select a lead compound as a starting point for further study and a determination whether one skilled in the art would have a reason to modify the lead compound to arrive at the claimed compound. Based on this analysis, appellants argue the rejection fails to establish that a person skilled in the art would have had a reason to select the oligonucleotides of Uhlmann for further investigation and argues that a person skilled in the art would not have had a reason to modify the compounds of Uhlmann to arrive at the instant oligomeric compounds

In response to the arguments regarding the two step analysis set forth by the Federal Circuit, the examiner notes that the fact patterns of the cited court decisions are quite different from those at issue in the instant application. Each of *Takeda*, *Eisai* and *Proctor & Gamble* is concerned with the obviousness of taking a teaching of one small molecule "A" and changing it to a new small molecule "B". However, the instant claims are not directed to a "lead compound" and the rejection is not based on the

transformation of one compound into a different molecule. Uhlmann et al. teach a genus of compounds which contains the features of a 5' phosphomonoester and a 5' mercaptonucleoside and the rejection describes why producing an oligonucleotide having the 3' hydroxyl moiety lacking in Uhlmann et al. would be obvious.

Appellants argue the rejection does not explain why a person seeking to develop antisense compounds would specifically focus on the compounds of Uhlmann, asserting that because there was a broad selection of possibilities in the art, the Examiner is required (based on *Takeda*) to show why a person skilled in the art would have had a reason to specifically single out the compounds of Uhlmann for further study.

The examiner notes that the rejection is not based on "singling out" Uhlmann for further study; in contrast to *Takeda*, the instant claims are not directed to a lead compound that has been modified to produce a different molecule, the relevant features of the instant claims, the 5' mercapto phosphomonoester, are found in Uhlmann.

Appellants argue Uhlmann discloses a broad genus and to provide the claimed compounds one would have to select a particular subgenus of these compounds and then modify the subgenus in a manner contrary to the teachings of Uhlmann. Appellants argue that to arrive at the instantly claimed compounds one must choose variables R^1, V, Q, Y, U and W from Uhlmann and the rejection does not establish why one would carry out the required modifications.

Appellants note that Q is not defined at column 3; it appears this variable is defined in column 3 as "a", which is not present in the formula. This interpretation is consistent with claim 1 of Uhlmann, which contains oxygen at the Q position.

While appellants argue the claimed compounds are dissimilar to those of Uhlmann, both the disclosure of Uhlmann and the knowledge of the person of ordinary skill in the art lead one to choose an oxo substituent for variables Q, Y, U and W. Claim 1 of Uhlmann specifies that Q is oxygen and Uhlmann also teaches at column 4 that Y, U and W are preferably oxygen. Also, those of ordinary skill in the art know that for each of these positions oxygen is the conventional substituent; that which occurs in unmodified DNA and RNA nucleotides. With regard to variable V, Uhlmann teaches only three possible values for this substituent, a sufficiently small genus that one of ordinary skill could immediately envisage the compounds embraced by this definition. Also, the teachings of Uhlmann are not viewed in isolation, the rejection is based on a combination of references and the art of Sproat would lead one to a thio substituent at this position of the terminus. While Uhlmann defines the variable R^1 more broadly than the instant claims, the teachings of the combined references serve to lead the person of ordinary skill to choose R^1 as a phosphate group. Both Kostenko et al. and Hamma et al. teach the usefulness of oligonucleotides comprising phosphate groups, providing reason to make such oligonucleotides and an expectation that such synthesis would be performed with predictable results.

Appellants argue that the compounds prepared by Uhlmann each had a 3' phosphoryl residue and only those with a 3' phosphate were active in the HSV-1 assay performed by Uhlmann. Appellants further argue Uhlmann does not provide specific teaching of oligomeric compounds having a 5' thiophosphate group or a phosphorus group attached to the oligomeric compound with a sulfur atom, noting that a number of

oligonucleotides were prepared with 3' terminal phosphoryl residues but none with a 5' phosphoryl residue.

This is incorrect; Uhlmann teaches 5' thiophosphate group and 5' mercapto nucleotides in formula I. It is true Uhlmann does not synthesize and test such molecules, but the teachings of the prior art are not limited to the exemplified embodiments. The Kostenko and Hamma references demonstrate the desirability and utility of 5' phosphorylated oligonucleotides and the ability of those in the art to synthesize such compounds.

Appellants argue that because all of the compounds of formula I of Uhlmann contain 3' phosphoryl groups, a person skilled in the art would not have had any reason to pursue the instantly recited limitation that the 3' terminus is hydroxyl or protected hydroxyl.

This argument is not persuasive because the combined references, including Uhlmann, teach that the standard chemistry for oligonucleotide synthesis provides 3' hydroxyl termini and that synthesis of such oligonucleotides is conventional.

Appellants argue that Kostenko and Hamma do not provide an expectation of success with regard to the required modifications of Uhlmann because they are not relevant art, being directed to oligonucleotides containing phosphates, not thiophosphates. Appellants further argue these references disclose particular advantages of the 5' phosphate as an intermediate group but not the advantages of an oligomeric compound having a 5' phosphate or a 5' thiophosphate as the final

compound. Appellants argue the instant compounds are useful with the 5' thiophosphate, either in pure form or as a composition.

These arguments are not persuasive because the instant claims are not limited to use as "final compounds", but could be used in the same way as the phosphate-containing oligonucleotides of Kostenko and Hamma. These references are cited to provide reason why one would make compounds with a 5' phosphate, i.e., why one would choose phosphate as the R^1 substituent of Uhlmann. The instant claims are in no way limited to use as final compounds for biological testing, but could be used as intermediates in the same fashion as the compounds of Kostenko and Hamma.

Appellants appear to misunderstand the examiner's statements in the final action regarding equivalence of sulfur and oxygen. The examiner states the usefulness of a 5' terminal phosphate is not expected to change based on how this group is attached to the oligonucleotide because oxygen and sulfur are equivalent and interchangeable. The appellants disagree by noting that replacement of oxygen with sulfur can have a significant effect on the properties of an oligomeric compound, for example the properties of nuclease resistance, protein binding, RNaseH activity and translation inhibition.

The statements regarding the equivalence of oxygen and sulfur were referring to the similarities of the chemical properties of these two elements, not the biological properties of compounds containing sulfur. These statements were made with regard to the usefulness of thiophosphates and whether it would be expected that thiophosphates could be used in the manner taught by Kostenko and Hamma for phosphates; the

biological properties of sulfur-containing oligonucleotides are not at issue. Chemically, oxygen and sulfur are considered equivalent because they can be readily interchanged, as evidenced by the ability of sulfur to be substituted for oxygen in a phosphate group. As stated before, a thiophosphate would be expected to have the same uses (such as those exemplified by Kostenko and Hamma) as an unsubstituted phosphate group.

With regard to the Sproat reference, appellants argue this reference provides teaching of a 5'-S protected nucleoside that can be added to the 5' end of an oligonucleotide to give a free 5'-thiol group which can be coupled to a wide variety of reagents. Appellants argue, however, that Sproat does not teach the use of these phosphoramidites at any position except at the 5'-position, does not teach the preparation of a 5' thiophosphate, and that use of this phosphoramidite would not produce the instantly claimed compounds as only the terminal 5'-thiophosphate has a sulfur atom attached to 5'-position.

These arguments are not persuasive because while the examiner recognizes that Sproat does not teach the preparation of a 5' thiophosphate, the rejection is not based only on this reference, but on the teachings of all cited references. Appellants are exactly correct: the inclusion of the phosphoramidite of Sproat at the 5' end of a nucleoside will produce a free thiol. If this oligonucleotide is then phosphorylated, for example to provide the "affinity handle" suggested by Hamma, this would provide the claimed compound.

Appellants argue the statement that an oligonucleotide having a 5' thiophosphate is a matter of design choice is a conclusory statement that does not support an

obviousness determination. Appellants argue, based on the finding in *In re Abbott*, that one skilled in the art would have been faced with many possible modifications because there are a vast number of chemistries and configurations of those chemistries available for modifying oligonucleotides and conclude that these chemistries and the cited references do not provide a "finite number of identified, predictable solutions."

The examiner disagrees; the cited references do provide a finite number of identified, predictable solutions. As noted above, Uhlmann teaches a genus of compounds that includes 5' thiophosphates. As stated above, the variables that must be chosen to obtain 5' thiophosphates from this genus are few and the teachings of the secondary references lead one to choose a phosphate at the 5' terminus, to choose a 5' mercapto nucleotide and to make the oligonucleotide with a 3' hydroxyl group.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635

Conferees:

/JD Schultz/

Supervisory Patent Examiner, Art Unit 1635

/Joseph T. Woitach/

Supervisory Patent Examiner, Art Unit 1633